

**REMARKS/ARGUMENTS.**

The subject matter of claim 7 has been cognated into revised claim 1. The phrase "linked to" has also been used in claim 1 to clarify the claim scope. Basis can be found in the specification at page 6 lines 13-15 and page 6 line 29 to page 7 line 8.

Claim 1 has also been amended to include the phrase "in a suitable solvent". Basis can be found throughout the specification, where eg. <sup>68</sup>Ga radioisotope in eluate from a radioisotope generator is used. See also page 8 line 7 to page 10 line 6 of the specification, plus Examples 1b, 2b and 3b.

Claim 7 has also been cancelled. The dependency of claim 8 has consequently been corrected.

Claims 1-3, 5 and 8-16 are now therefore pending in the application.

**1. CLAIM REJECTIONS.**

Claims 1, 5 and 7 stand newly rejected for use of inconsistent terminology with respect to the chelating agent. Claim 7 has been cancelled. Claim 5 has been amended to provide proper antecedent basis. The objection in this regard should therefore be withdrawn.

**2. CLAIM REJECTIONS: 35 USC §112.**

Claim 7 stands rejected in this regard. The objected to phrase has been deleted from the language of claim 7 (now part of amended claim 1). The objection should therefore be withdrawn.

**3. CLAIM REJECTIONS: 35 USC §103.**

Claims 1-3, 5 and 7-15 stand rejected as being unpatentable over Griffiths (WO 03/059397) in view of Yngve [Int.Diss.Abs., 62 (2001)], Bottcher (US 5,439,863) and Lidstrom [Tet.Lett., 57, 9225-9283 (2001)] and in further view of Maier-Borst (GB 2056471 A) and Wheaton [Industr.Eng.Chem., 43, 1088-1093 (1951)].

Applicants first of all suggest that an obviousness rejection which relies on features taken from 6 references, spanning a timespan of over 50 years, and in diverse scientific disciplines cannot in reality represent an 'obvious combination'. Applicants contend that it is unrealistic for the thinking of the person skilled in the art to be portrayed in this scatter-gun manner. The person skilled in the art could logically contemplate combining 2 references but 6 is too many. The very fact that 6 references are needed to construct the objection is evidence of an invalid, hindsight analysis based on piecemeal reconstruction of claim features.

The Examiner alleges that the person skilled in the art would find it obviously desirable to use microwave activation to accelerate and make more reproducible the <sup>68</sup>Ga complexation of the conjugates of Griffiths. The Examiner relies on Bottcher and Lidstrom (the latter newly cited) to provide the microwave activation aspect of present claim 1.

Applicants disagree with that analysis. Applicants point out that "the prior art itself must provide a motivation or reason for the worker in the art, without the benefit of the Applicant's specification, to make necessary changes in the reference device". See, *Ex parte*

*Chicago Rawhide Manufacturing Co.*, 226 U.S.P.Q. 438 (PTO Bd. App. 1984). As argued previously, there is no teaching in Bottcher of successfully applying microwave activation in coordination chemistry. The Examiner rejects that counter-argument (at 28-29 pages 10-11) and asserts that "...the use of microwave activation does not need to be exemplified".

Applicants find that statement illogical – the Examiner is relying on Bottcher to provide the alleged motivation for the person skilled on the art to apply microwave activation to metal complexation reactions, in particular radiometal complexation, yet suggests that any tangible evidence of success from Bottcher is immaterial.

Applicants suggest that is unrealistic – the person skilled in the art would know that the use of microwave ovens can present a serious safety hazard, eg. due to the heating of organic solvents leading to high pressures and explosions. The Examiner is effectively suggesting that the person skilled in the art would take a huge risk in combining Griffiths/Bottcher and not worry about the uncertainties and consequences. Lidstrom (cited by the Examiner) alludes to the risks of microwave ovens at page 9226 (left hand column paragraph 2):

"This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low understanding of the basics of microwave dielectric heating."  
and at page 9231 (right hand column, 2<sup>nd</sup> parag):

“The lack of control in domestic microwave ovens when performing assisted synthesis has led to a vast number of incidents, including explosions, being reported.”

At the priority date of the present invention, based on Bottcher alone and without sight of the present invention, the person skilled in the art could not know that it would be safe to proceed, let alone have a realistic expectation of success. There would thus be considerable doubt as to whether the method of Bottcher could be applied (i) safely and (ii) successfully, to radiometal reactions without tangible evidence.

There is also the substantial doubt as to whether what Bottcher applies on the kilogramme scale could be successfully translated to the microgramme scale – i.e. at several orders of magnitude lower concentration. In the real world, the person skilled in the art would face those issues so applicants contend that the lack of evidence of success in Bottcher is (and must be) material to the argument.

For the reaction scale issue, the Examiner rejects applicants’ previous argument (at 21) on the grounds that Bottcher was not relied on to teach the amounts involved and that the present claims do not specify the amounts. That misses the point – the Examiner wishes to rely on Bottcher, but cannot choose to ignore the clear teaching on scale applied by Bottcher itself. The Examiner cannot artificially divorce the teaching of Bottcher on scale from the teaching of Bottcher as whole. In addition, the Examiner has not addressed applicant’s key point which is that the scale of Bottcher is incompatible with that of both Griffiths and Yngve (because it is incompatible with radiopharmaceuticals in general).

Furthermore, applicants also point out that the present claims do not need to specify the amounts involved. The patent is directed to the person skilled in the art of radiopharmaceuticals. That person would know that the agents of present claim 1 would simply not be handled on a kilogramme scale. The Examiner has failed to justify why the person skilled in the art would lack considerable uncertainty as to whether the theoretical teaching of Bottcher could be applied for radiochemistry (both safely and effectively) at several orders of magnitude lower concentration. The person skilled in art would know that the safety risk with radioisotopes is of course much greater the greater the scale, due to radiation dose, risk of contamination, risk of radiolysis of the materials at higher radiation concentration etc. These serious issues in the field of radiopharmaceuticals simply cannot be ignored, since they are facets of the field of technology.. The presence of that serious doubt in applicant's view cannot be dismissed, since it provides a powerful disincentive to combine.

In the real world, the person skilled in art could therefore have no motivation to combine Griffiths/Bottcher for the reasons given above. The Examiner is invited to reconsider her position on this point. The Griffiths/Bottcher combination is believed improper and the rejection based on the combination should be withdrawn.

The Examiner also newly cites Lidstrom page 9267 (5.11 Organometallic reactions) as suggested evidence that a “metal-macrocyclic chelate may be generated *via* the microwave technique...”.

Firstly, applicants point out that the reaction reference to in Lidstrom refers to Reference 521 therein. A copy of that reference is provided – Shaabani [J.Chem.Res., 672-6773 (1998)]. It refers to a microwave reaction without solvent. The person skilled in the art would know that such a reaction is not suitable for the process of present claim 1. In order to clarify this point claim 1 now specifies that a ‘suitable solvent’ is used. Hence, the combination Griffiths/Lidstrom or Yngve/Lidstrom does not lead to subject matter within the scope of present claim 1, since it teaches towards solvent-free reactions outside the scope of the present claims.

Secondly, applicants point out that the citation from Lidstrom does in fact clearly refer to what the person skilled in the art would recognize as a “metal template synthesis”. In such reactions, the macrocyclic chelate (in the case of Lidstrom, a phthalocyanine) does not exist at the start of the reaction, but is synthesized during the reaction. The presence of a metal ion helps to drive the reaction to completion, since the reactants involved coordinate to the metal, and typically react together whilst coordinated to the metal. Such chelator template synthesis is completely different from the subject matter of the present invention, wherein a pre-formed/pre-existing macrocyclic chelate is linked to a “targeting vector” and the radiogallium metal complex is formed from the same conjugated chelator. Hence, when

the teaching of Lidstrom is properly focused on what the reference itself actually teaches, Lidstrom is silent on the use of microwave radiation to facilitate a reaction of the type:



In addition, in this analysis the logical combination of Griffiths/Lidstrom or Yngve/Lidstrom teaches towards a 'metal template synthesis' for forming the metal complex. Such chemistry is outside the scope of present claim 1. The logical combination therefore teaches away from present claim 1.

Hence, when properly construed the combination of Griffiths/Lidstrom or Yngve/Lidstrom does not provide the subject matter of present claim 1. The rejection to claim 1 based on those combinations should therefore be withdrawn.

Applicants point out that only Bottcher and Lidstrom of the prior art cited teach microwave activation. Applicants believe that, for the reasons given above, neither reference is properly combinable with Griffiths and/or Yngve. The combination of references therefore does not lead in an obvious manner to the subject matter of present claim 1. The obviousness rejection to claim 1 should therefore be withdrawn

Claims 2-3, 5 and 8-15 are all dependent on claim 1, and are hence by definition also believed non-obvious over the prior art cited. The inventive step objection should therefore be withdrawn.

**4. DOUBLE PATENTING.**

Claims 1-3, 5 and 7 and 15 are provisionally rejected in this regard over corresponding application USSN 10/552206.

Claims 1-3, 5 and 7 and 15 provisionally rejected in this regard over corresponding application USSN 111/358681.

Applicants will file a suitable terminal disclaimer in the event that this application is deemed allowable.

**CONCLUSION.**

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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